



## Synthesis and *in vitro* Biological Evaluation of a Series of 5-Benzylidene Derivatives of Rhodanine-Sulfonylurea Hybrid as a Novel Class of $\alpha$ -Glucosidase Inhibitors

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A novel rhodanine-sulfonylurea hybrid (**C**) has been prepared based on the isocyanate-amine reaction conditions in the first step and its 5-benzylidene analogues (**C1-C13**) were synthesized using Knoevenagel reaction conditions as the subsequent step. The physical and spectral characterization of all the synthesized compounds (**C-C13**) was performed using FT-IR, <sup>1</sup>H NMR and HR-ESI-MS spectral methods. All compounds were subjected to *in vitro*  $\alpha$ -glucosidase enzyme inhibitory properties at 100  $\mu$ M concentration. The results were compared with a standard drug, voglibose, also tested at the similar concentrations. The bioassay results revealed that the intermediate compound **C** was more potent with a percentage inhibitory activity of 64.86%, which is relatively better than the series of 5-benzylidene analogues (**C1-C13**) synthesized from the intermediate **C**. This clearly displayed that substitution at position-5 on the rhodanine ring of intermediate **C** is not a favourable substitution to enhance the bioactivity; however, one of the derivative compounds, **C12**, exhibited potency of 58.32%, which is close to the compound **C**. It is significant that both the intermediate **C** and compound **C12** displayed better potency compared to the standard voglibose, with percentage inhibition recorded at 37.75%. The additive or synergistic potential of the bioactive pharmacophore tosylurea, which was earlier established, tolerated the rhodanine ring substitution towards retaining the  $\alpha$ -glucosidase inhibitory properties.

**Keywords:** Rhodanine, Sulfonylurea, Rhodanine-Sulfonylurea hybrid, 5-Benzylidene-rhodanine,  $\alpha$ -Glucosidase inhibitor.

### INTRODUCTION

Diabetes mellitus represents a chronic metabolic condition marked by deficient glucose homeostasis, resulting from diminished insulin secretion and the presence of insulin resistance [1]. Inadequate insulin leads to hyperglycaemia, potentially causing severe health complications [2]. The prevalence of diabetes is projected to significantly rise, emphasizing the need for improved treatment options [3]. Current diabetes drugs face challenges, driving ongoing efforts in drug discovery [4]. Medicinal chemists are actively developing innovative compounds to enhance diabetes management [5]. The search for novel drug candidates in diabetes research is crucial to address the evolving healthcare demands of individuals with this complex disorder [6].

$\alpha$ -Glucosidase is a vital enzyme involved in the digestion of carbohydrates, breaking them down into simpler sugars like glucose [7]. This enzyme, predominantly located in the small intestine, plays a crucial role in the final stages of carbohydrate digestion before absorption into the bloodstream. Inhibiting  $\alpha$ -glucosidase can slow down the digestion and absorption of carbohydrates, leading to a more controlled release of glucose into the blood. This inhibition is particularly beneficial for individuals with Type 2 diabetes mellitus, helping to regulate blood sugar levels and reduce the risk of postprandial hyperglycaemia [8]. The inhibition of  $\alpha$ -glucosidase is a fundamental therapeutic strategy in managing conditions such as diabetes mellitus. By impeding the breakdown of complex carbohydrates into glucose,  $\alpha$ -glucosidase inhibitors assist in managing postprandial blood glucose levels [9]. This is crucial in preven-

ting sudden spikes in blood sugar levels after meals, which can contribute to the development of long-term complications associated with diabetes, including cardiovascular diseases and neuropathy [10]. Commonly prescribed  $\alpha$ -glucosidase inhibitors like acarbose, voglibose and miglitol function by competitively binding to the active site of  $\alpha$ -glucosidase [11]. This binding reduces the rate of carbohydrate digestion and glucose absorption, aiding in the control of blood sugar levels [12]. The use of these inhibitors is a well-established approach in the treatment of Type 2 diabetes mellitus, offering a means to manage blood glucose levels effectively and mitigate the risks associated with uncontrolled postprandial hyperglycaemia [13].

Rhodanine is a five-membered heterocyclic compound containing sulfur and nitrogen at 1<sup>st</sup> and 3<sup>rd</sup> positions, respectively. Position-5 of the ring, which has a reactive methylene group, is one of the positions to explore for chemical diversity with respect to their bioactive potential. Position 3 is a secondary nitrogen that can be further alkylated with various substituents [14]. Rhodanine is also a privileged scaffold extensively studied by researchers; one of the most popular clinically used rhodanine based antidiabetic drugs is epalrestat [15]. The derivatives of rhodanine revealed various bioactive profiles reported in the literature, such as antioxidant [16], topoisomerase II inhibitors [17], tyrosinase inhibitors [18], HCV NS3 protease inhibitor [19], pentose phosphate pathway enzymes inhibitors [20], antimicrobial activity [21], JSP-1 inhibitors [22], *Mycobacterium tuberculosis* InhA inhibitors [23], metallo- $\beta$ -lactamase inhibitors [24], cholinesterase inhibitors [25], anti-leukemia agents [26], anticancer [27], IKK $\beta$  inhibitors [28], HIV-1 integrase inhibitors [29], hepatitis C virus NS5B polymerase [30], anti-apoptotic protein Bcl-2 inhibitors [31], carbonic anhydrase inhibitor [32], dual cyclooxygenase-1/2 and 5-lipoxygenase inhibitors [33], DNA gyrase B inhibitors [34], anxiety- and depressive-like states [35], cholesterol esterase inhibitors [36], inhibitors of *Escherichia coli* deoxyxylulose phosphate reductoisomerase (DXR) [37] and antibacterial agents [38], respectively.

Equally, sulfonylureas are well known; which were first ever discovered as oral antidiabetic agents. There are several generations such as first, second and third-generation compounds, that were developed and received approval for clinical use [39,40]. In addition, sulfonylurea-based herbicides also captured the attention of researchers and several products were approved to improve crop production. The key pharmacophore is sulfonyl-urea. The medicinal chemists explored its chemical and biological properties by substituting sulfonyl or urea moieties towards the development of new therapeutics. Several literature reports show that the chemical diversity leads to biological diversity as well that include anticancer [41], hypoglycemic [42], antagonists of CXCR2 receptor [43], antimalarial [44], reversible inhibitors of human steroid sulfatase [45], vasodilator [46], selective antagonists of the TP $\alpha$  and TP $\beta$  isoforms of human thromboxane A2 receptor [47], herbicidal [48], oncolytic [49], KATP-channel openers [50], antimicrobial [51], *Vibrio fischeri* quorum sensing regulator [52], peroxisome proliferator activated receptor  $\gamma$ -agonistic [53], selective EP4 receptor antagonists [54], selective

bombesin receptor subtype-3 (SCS-3) agonist [55], inhibitors of aldehyde dehydrogenase [56] and cytotoxic [57], respectively,

In continuation to our studies focused on discovering novel  $\alpha$ -glucosidase inhibitors, this study reported the synthesis and characterization of a series of novel 5-benzylidene derivatives (C1-C13) of the rhodanine-sulfonylurea hybrid (C) as novel class of  $\alpha$ -glucosidase inhibitors. Some of our earlier research outcomes showed that the sulfonylurea moiety often adds to a wide range of chemotypes and has strong  $\alpha$ -glucosidase inhibitory properties.

## EXPERIMENTAL

All the reagents and chemicals were purchased from Sigma-Aldrich, USA, which includes 3-aminorhodanine, benzaldehyde, tosylisocyanate, 4-dimethylaminobenzaldehyde, 3-methoxybenzaldehyde, 2,4-dimethoxybenzaldehyde, 2-/3-/4-chlorobenzaldehyde, 2-/3-/4-fluorobenzaldehyde, 2-/3-/4-bromobenzaldehyde, piperidine, methylene chloride, acetone, hexane, LC grade methanol, ethyl acetate, absolute ethanol, dimethyl sulfoxide (DMSO), 4-nitrophenyl- $\alpha$ -D-glucopyranoside, respectively.

The purity of the synthesized compounds was checked on pre-coated 60 F<sub>254</sub> silica gel TLC plates (Merck, 0.25 mm) thickness by means of a gradient solvent system with *n*-hexane and ethyl acetate. Fourier-transform infrared (FT-IR) spectrometer (Shimadzu, Model: MIRAffinity-1S) used to record the spectra. <sup>1</sup>H NMR spectra recorded on a Varian NMR System (Varian, 500 MHz) using TMS as an internal standard, weighing balance (Mettler Toledo, Model: ML204) was used to weigh the chemicals used in the synthetic protocols. The electrospray ionization mass spectra (ESI-MS) were recorded using high-resolution mass spectrometry (HRMS) (Thermo-Scientific, Q Exactive Focus (Orbitrap LC-MS/MS System)). Melting point apparatus (Stuart Scientific, Model: SMP1) were determined in open capillary tubes and were uncorrected.

**Synthesis of rhodanine-sulfonylurea hybrid (C):** 3-Aminorhodanine (**1**, 0.020 mol) was dissolved in 10 mL of methylene chloride with constant stirring and the flask was warmed in a water bath for 15 min. The reaction was added with *p*-toluene-sulfonyl isocyanate (0.025 mol), followed by removal from the hot plate. The reaction mixture was gently stirred at room temperature for 10-15 min and the solution was cooled down to room temperature. The stirring continued until the mixture gradually solidified and formed a white powder, which is the intermediate compound **C** (Scheme-I). After washing the intermediate **C** with cold methanol under vacuum filtration. The crude compound was dried and directly used for the next step. Yield: 80%; white powder; m.p.: 182-186 °C; m.f.: C<sub>11</sub>H<sub>11</sub>N<sub>3</sub>O<sub>4</sub>S<sub>3</sub>; Relative molecular mass: 344; FT-IR (ATR,  $\nu_{\max}$ , cm<sup>-1</sup>): 3248.13 (2° amine N-H *str.*), 1701.22 (C=O *str.*), 1672.28 (2° amide NH *bend.*), 1517.98 (C=C *str.*), 1363.67 (SO<sub>2</sub>, *asym.*), 1163.06 (SO<sub>2</sub>, *sym.*), 1087.85 (C=S *str.*); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 2.35 (s, 3H, Ar-CH<sub>3</sub>), 4.20 (s, 2H, rhodanine-CH<sub>2</sub>), 7.26 (s, 1H, sulfonamido -SO<sub>2</sub>N-H), 7.34-7.41 (m, 2H, Ar-H), 7.68-7.82 (m, 2H, Ar-H), 9.51 (s, 1H, carboxamido -CON-H); ESI-HRMS (*m/z*): 343.9823 [M-H]<sup>-</sup> (negative-ion mode).

**Synthesis of 5-benzylidene derivatives of rhodanine-sulfonylurea hybrid (C1-C13):** 5-Benzylidene derivatives of rhodanine-sulfonylurea hybrid (C1-C13) were prepared by reacting equimolar concentration (0.001 mol) of intermediate C with a substituted benzaldehyde. The reaction vessel charged with both the reactants solubilized in 30 mL of ethanol. Catalytic amount of piperidine (10  $\mu$ L) was added to the reaction mixture and refluxed for 2-3 h. The reaction mixture was monitored using TLC for the completion of the product formation. Upon completion, the product was cooled in crushed ice bath, the precipitated compound was washed with distilled water and recrystallized with cold methanol to yield titled compounds C1-C13 (Scheme-I).

**(E)-N-((5-Benzylidene-4-oxo-2-thioxothiazolidin-3-yl)carbamoyl)-4-methylbenzenesulfonamide (C1):** Yield: 55%; yellow powder; m.p.: 190-193  $^{\circ}$ C; m.f.:  $C_{18}H_{15}N_3O_4S_3$ ; Relative molecular mass: 433; FT-IR (ATR,  $\nu_{max}$ ,  $cm^{-1}$ ): 3296.35 (2 $^{\circ}$  amine N-H *str.*), 1705.07 (C=O *str.*), 1585.49 (2 $^{\circ}$  amide NH *bend.*), 1571.99 (C=C *str.*), 1377.17 (SO<sub>2</sub>, *asym.*), 1122.57 (SO<sub>2</sub>, *sym.*), 1093.64 (C=S *str.*);  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 2.48 (s, 3H, Ar-CH<sub>3</sub>), 5.93 (s, 1H, carboxamido -CON-H), 7.51-7.65 (m, 9H, Ar-H), 7.84 (s, 1H, benzylidene -C=C-H); ESI-HRMS ( $m/z$ ): 432.0135 [M-H]<sup>-</sup> (negative-ion mode).

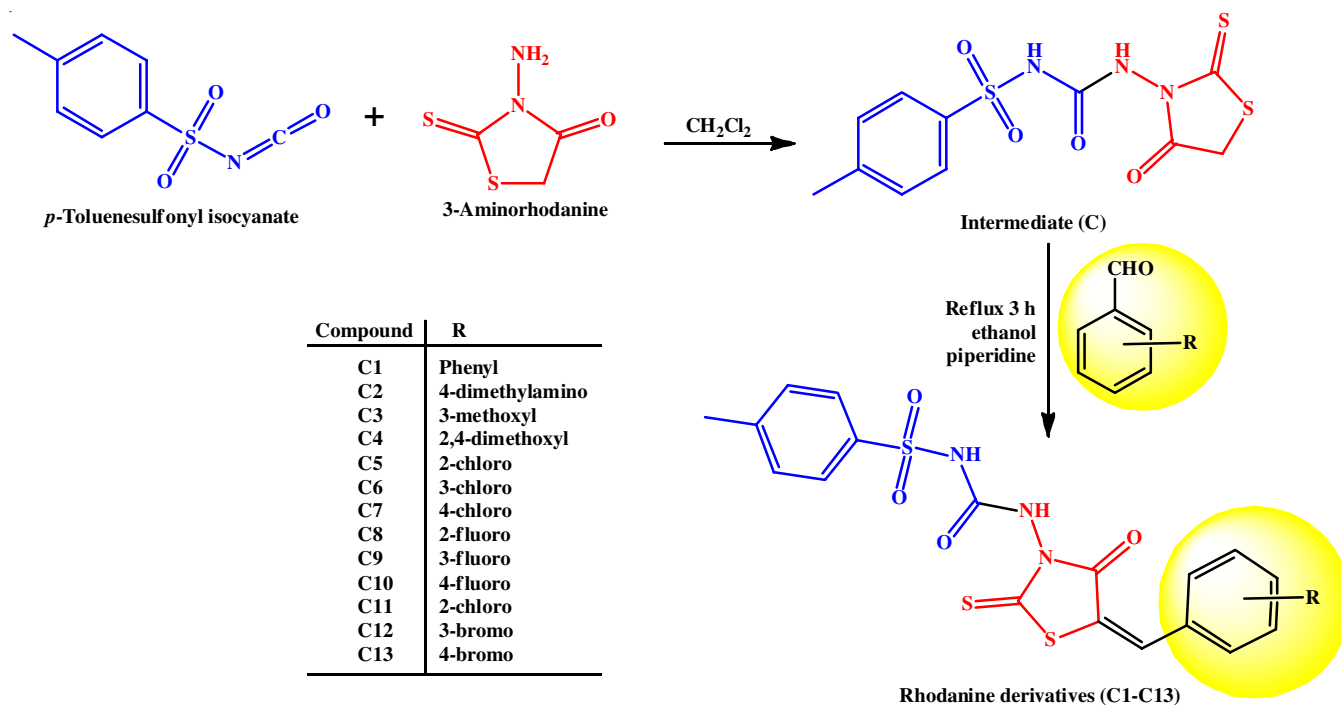
**(E)-N-((5-(4(Dimethylamino)benzylidene)-4-oxo-2-thioxothiazolidin-3yl)carbamoyl)-4-methylbenzenesulfonamide (C2):** Yield: 48%; yellow powder; m.p.: 210-214  $^{\circ}$ C; m.f.:  $C_{20}H_{20}N_4O_4S_3$ ; Relative molecular mass: 476; FT-IR (ATR,  $\nu_{max}$ ,  $cm^{-1}$ ): 3298.28 (2 $^{\circ}$  amine N-H *str.*), 1712.79 (C=O *str.*), 1527.62 (2 $^{\circ}$  amide NH *bend.*), 1612.49 (C=C *str.*), 1355.96 (SO<sub>2</sub>, *asym.*), 1112.93 (SO<sub>2</sub>, *sym.*), 1056.99 (C=S *str.*);  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 2.49 (s, 3H, Ar-CH<sub>3</sub>), 3.03 (s, 6H, Ar-N(CH<sub>3</sub>)<sub>2</sub>), 5.93 (s, 1H, sulfonamido -SO<sub>2</sub>N-H), 6.82-6.83 (d, 2H, Ar-H), 7.38-7.53 (m, 4H, Ar-H), 7.71 (s, 1H, benzyli-

dene -C=C-H), 7.92-7.96 (m, 2H, Ar-H); ESI-HRMS ( $m/z$ ): 475.0553 [M-H]<sup>-</sup> (negative-ion mode).

**(E)-N-((5-(3-Methoxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)carbamoyl)-4-methylbenzenesulfonamide (C3):** Yield: 45%; yellow powder; m.p.: 171-175  $^{\circ}$ C; m.f.:  $C_{19}H_{17}N_3O_5S_3$ ; Relative molecular mass: 463; FT-IR (ATR,  $\nu_{max}$ ,  $cm^{-1}$ ): 3288.63 (2 $^{\circ}$  amine N-H *str.*), 3213.41 (2 $^{\circ}$  amine N-H *str.*), 1680.00 (C=O *str.*), 1552.70 (2 $^{\circ}$  amide NH *bend.*), 1649.14 (C=C *str.*), 1375.25 (SO<sub>2</sub>, *asym.*), 1170.79 (SO<sub>2</sub>, *sym.*), 1043.49 (C=S *str.*);  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 2.49 (s, 3H, Ar-CH<sub>3</sub>), 3.82 (s, 3H, Ar-OCH<sub>3</sub>), 5.93 (s, 1H, sulfonamido -SO<sub>2</sub>N-H), 7.08-7.47 (m, 8H, Ar-H), 7.82 (s, 1H, benzylidene -C=C-H); ESI-HRMS ( $m/z$ ): 462.0247 [M-H]<sup>-</sup> (negative-ion mode).

**(E)-N-((5-(2,4-Dimethoxybenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)carbamoyl)-4-methylbenzenesulfonamide (C4):** Yield: 62%; yellow powder; m.p.: 191-195  $^{\circ}$ C; m.f.:  $C_{20}H_{19}N_3O_6S_3$ ; Relative molecular mass: 493; FT-IR (ATR,  $\nu_{max}$ ,  $cm^{-1}$ ): 3298.28 (2 $^{\circ}$  amine N-H *str.*), 3159.40 (2 $^{\circ}$  amine N-H *str.*), 1718.58 (C=O *str.*), 1697.36 (C=C *str.*), 1577.77 (2 $^{\circ}$  amide NH *bend.*), 1336.67 (SO<sub>2</sub>, *asym.*), 1147.65 (SO<sub>2</sub>, *sym.*), 1099.43 (C=S *str.*);  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 2.49 (s, 3H, Ar-CH<sub>3</sub>), 3.85-3.91 (d, 6H, 2  $\times$  Ar-OCH<sub>3</sub>), 5.91 (s, 1H, sulfonamido -SO<sub>2</sub>N-H), 6.68-6.72 (m, 4H, Ar-H), 7.39-7.41 (m, 3H, Ar-H), 7.90 (s, 1H, benzylidene -C=C-H); ESI-HRMS ( $m/z$ ): 492.0345 [M-H]<sup>-</sup> (negative-ion mode).

**(E)-N-((5-(2-Chlorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)carbamoyl)-4-methylbenzenesulfonamide (C5):** Yield: 51%; yellow powder; m.p.: 171-174  $^{\circ}$ C; m.f.:  $C_{18}H_{14}N_3O_4S_3Cl$ ; Relative molecular mass: 466; FT-IR (ATR,  $\nu_{max}$ ,  $cm^{-1}$ ): 3030.17 (2 $^{\circ}$  amine N-H *str.*), 1707.00 (C=O *str.*), 1591.27 (C=C *str.*), 1309.67 (SO<sub>2</sub>, *asym.*), 744.52 (C-Cl *str.*);  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 2.48 (s, 3H, Ar-CH<sub>3</sub>),



Scheme-I: Synthetic route of 5-benzylidene analogues of rhodanine-sulfonylurea hybrid (C-C13)

7.54-7.69 (m, 7H, Ar-H), 7.96 (s, 1H, benzylidene -C=C-H), 8.18-8.19 (d, 1H, Ar-H), 9.34 (s, 1H, carboxamido -CON-H); ESI-HRMS ( $m/z$ ): 465.9746 [M-H]<sup>-</sup> (negative-ion mode).

**(E)-N-((5-(3-Chlorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)carbamoyl)-4-methylbenzenesulfonamide (C6):** Yield: 59%; yellow powder; m.p.: 188-191 °C; m.f.: C<sub>18</sub>H<sub>14</sub>N<sub>3</sub>O<sub>4</sub>S<sub>3</sub>Cl; Relative molecular mass: 466; FT-IR (ATR,  $\nu_{\max}$ , cm<sup>-1</sup>): 3300.20 (2° amine N-H *str.*), 1714.72 (C=O *str.*), 1602.85 (C=C *str.*), 1365.60 (SO<sub>2</sub>, asym.), 669.30 (C-Cl *str.*); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 2.48 (s, 3H, Ar-CH<sub>3</sub>), 5.93 (s, 1H, sulfonamido -SO<sub>2</sub>N-H), 7.56-7.72 (m, 8H, Ar-H), 7.83 (s, 1H, benzylidene -C=C-H); ESI-HRMS ( $m/z$ ): 465.3001 [M-H]<sup>-</sup> (negative-ion mode).

**(E)-N-((5-(4-Chlorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)carbamoyl)-4-methylbenzenesulfonamide (C7):** Yield: 38%; yellow powder; m.p.: 208-211 °C; m.f.: C<sub>18</sub>H<sub>14</sub>N<sub>3</sub>O<sub>4</sub>S<sub>3</sub>Cl; Relative molecular mass: 466; FT-IR (ATR,  $\nu_{\max}$ , cm<sup>-1</sup>): 3286.63 (2° amine N-H *str.*), 1710.86 (C=O *str.*), 1581.63 (C=C *str.*), 1363.67 (SO<sub>2</sub>, asym.), 518.85 (C-Cl *str.*); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 2.49 (s, 3H, Ar-CH<sub>3</sub>), 7.59-7.66 (m, 8H, Ar-H), 7.84 (s, 1H, benzylidene -C=C-H); ESI-HRMS ( $m/z$ ): 465.9768 [M-H]<sup>-</sup> (negative-ion mode).

**(E)-N-((5-(2-Fluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)carbamoyl)-4-methylbenzenesulfonamide (C8):** Yield: 42%; yellow powder; m.p.: 153-157 °C; m.f.: C<sub>18</sub>H<sub>14</sub>N<sub>3</sub>O<sub>4</sub>S<sub>3</sub>F; Relative molecular mass: 451; FT-IR (ATR,  $\nu_{\max}$ , cm<sup>-1</sup>): 3393.00 (2° amine N-H *str.*), 1707.00 (C=O *str.*), 1602.85 (C=C *str.*), 1570.00 (2° amide NH *bend.*), 1314.00 (SO<sub>2</sub>, asym.), 1152.00 (SO<sub>2</sub>, sym.), 1228.66 (C-F *str.*); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 2.45 (s, 3H, Ar-CH<sub>3</sub>), 7.40-7.46 (m, 4H, Ar-H), 7.59-7.63 (m, 2H, Ar-H), 7.72-7.76 (m, 1H, Ar-H), 7.82 (s, 1H, benzylidene -C=C-H), 8.08-8.11 (t, 1H, Ar-H), 9.17 (s, 1H, carboxamido -CON-H); ESI-HRMS ( $m/z$ ): 450.0033 [M-H]<sup>-</sup> (negative-ion mode).

**(E)-N-((5-(3-Fluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)carbamoyl)-4-methylbenzenesulfonamide (C9):** Yield: 63%; yellow; m.p.: 177-182 °C; m.f.: C<sub>18</sub>H<sub>14</sub>N<sub>3</sub>O<sub>4</sub>S<sub>3</sub>F; Relative molecular mass: 451; FT-IR (ATR,  $\nu_{\max}$ , cm<sup>-1</sup>): 3292.49 (2° amine N-H *str.*), 1703.14 (C=O *str.*), 1577.77 (C=C *str.*), 1570.00 (2° amide NH *bend.*), 1355.96 (SO<sub>2</sub>, asym.), 1121.00 (SO<sub>2</sub>, sym.), 1247.94 (C-F *str.*); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 2.49 (s, 3H, Ar-CH<sub>3</sub>), 5.93 (s, 1H, sulfonamido -SO<sub>2</sub>N-H), 7.34-7.38 (t, 2H, Ar-H), 7.45-7.46 (d, 2H, Ar-H), 7.50-7.52 (d, 2H, Ar-H), 7.57-7.62 (q, 2H, Ar-H), 7.84 (s, 1H, benzylidene -C=C-H); ESI-HRMS ( $m/z$ ): 450.0030 [M-H]<sup>-</sup> (negative-ion mode).

**(E)-N-((5-(4-Fluorobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)carbamoyl)-4-methylbenzenesulfonamide (C10):** Yield: 31%; yellow powder; m.p.: 195-200 °C; m.f.: C<sub>18</sub>H<sub>14</sub>N<sub>3</sub>O<sub>4</sub>S<sub>3</sub>F; Relative molecular mass: 451; FT-IR (ATR,  $\nu_{\max}$ , cm<sup>-1</sup>): 3292.49 (2° amine N-H *str.*), 1701.22 (C=O *str.*), 1577.77 (C=C *str.*), 1595.13 (2° amide NH *bend.*), 1354.03 (SO<sub>2</sub>, asym.), 1242.16 (C-F *str.*), 1121.00 (SO<sub>2</sub>, sym.); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 2.49 (s, 3H, Ar-CH<sub>3</sub>), 5.93 (s, 1H, sulfonamido -SO<sub>2</sub>N-H), 7.37-7.41 (dd, 4H, Ar-H), 7.71-7.73 (dd, 4H, Ar-H), 7.86 (s, 1H, benzylidene -C=C-H); ESI-HRMS ( $m/z$ ): 450.0028 [M-H]<sup>-</sup> (negative-ion mode).

**(E)-N-((5-(2-Bromobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)carbamoyl)-4-methylbenzenesulfonamide (C11):** Yield: 66%; yellow powder; m.p.: 159-165 °C; m.f.: C<sub>18</sub>H<sub>14</sub>N<sub>3</sub>O<sub>4</sub>S<sub>3</sub>Br; Relative molecular mass: 512; FT-IR (ATR,  $\nu_{\max}$ , cm<sup>-1</sup>): 3292.49 (2° amine N-H *str.*), 1726.29 (C=O *str.*), 1581.63 (C=C *str.*), 1557.00 (2° amide NH *bend.*), 1355.96 (SO<sub>2</sub>, asym.), 1117.00 (SO<sub>2</sub>, sym.), 657.73 (C-Br *str.*); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 2.48 (s, 3H, Ar-CH<sub>3</sub>), 5.93 (s, 1H, sulfonamido -SO<sub>2</sub>N-H), 7.42-7.45 (m, 2H, Ar-H), 7.55-7.59 (m, 4H, Ar-H), 7.81-7.83 (d, 2H, Ar-H), 7.88 (s, 1H, benzylidene -C=C-H); ESI-HRMS ( $m/z$ ): 511.9212 [M-H]<sup>-</sup> (negative-ion mode).

**(E)-N-((5-(3-Bromobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)carbamoyl)-4-methylbenzenesulfonamide (C12):** Yield: 61%; yellow powder; m.p.: 192-197 °C; m.f.: C<sub>18</sub>H<sub>14</sub>N<sub>3</sub>O<sub>4</sub>S<sub>3</sub>Br; Relative molecular mass: 512; FT-IR (ATR,  $\nu_{\max}$ , cm<sup>-1</sup>): 3302.13 (2° amine N-H *str.*), 1705.07 (C=O *str.*), 1556.55 (C=C *str.*), 1557.00 (2° amide NH *bend.*), 1369.46 (SO<sub>2</sub>, asym.), 1126.00 (SO<sub>2</sub>, sym.), 667.37 (C-Br *str.*); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 2.49 (s, 3H, Ar-CH<sub>3</sub>), 5.93 (s, 1H, sulfonamido -SO<sub>2</sub>N-H), 7.48-7.52 (t, 3H, Ar-H), 7.60-7.71 (dd, 3H, Ar-H), 7.83 (s, 2H, Ar-H), 7.87 (s, 1H, benzylidene -C=C-H); ESI-HRMS ( $m/z$ ): 511.9237 [M-H]<sup>-</sup> (negative-ion mode).

**(E)-N-((5-(4-Bromobenzylidene)-4-oxo-2-thioxothiazolidin-3-yl)carbamoyl)-4-methylbenzenesulfonamide (C13):** Yield: 51%; yellow powder; m.p.: 215-220 °C; m.f.: C<sub>18</sub>H<sub>14</sub>N<sub>3</sub>O<sub>4</sub>S<sub>3</sub>Br; Relative molecular mass: 512; FT-IR (ATR,  $\nu_{\max}$ , cm<sup>-1</sup>): 3286.70 (2° amine N-H *str.*), 1703.14 (C=O *str.*), 1577.77 (C=C *str.*), 1560.00 (2° amide NH *bend.*), 1363.67 (SO<sub>2</sub>, asym.), 1126.00 (SO<sub>2</sub>, sym.), 516.92 (C-Br *str.*); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 2.48 (s, 3H, Ar-CH<sub>3</sub>), 5.93 (s, 1H, sulfonamido -SO<sub>2</sub>N-H), 7.57-7.59 (d, 4H, Ar-H), 7.73-7.75 (d, 4H, Ar-H), 7.82 (s, 1H, benzylidene -C=C-H); ESI-HRMS ( $m/z$ ): 511.9226 [M-H]<sup>-</sup> (negative-ion mode).

**in vitro  $\alpha$ -Glucosidase inhibitor screening:** The  $\alpha$ -glucosidase inhibitory activity of compounds (C-C13) were evaluated using *in vitro*  $\alpha$ -glucosidase enzymatic kinetics. The biological assay consumables include enzyme: *Saccharomyces cerevisiae* Type 1, substrate: 4-nitrophenyl  $\alpha$ -D-glucopyranoside, standard: voglibose (as standard drug) and test: compounds C-C13 (100  $\mu$ M), buffer: phosphate buffer (pH 7.3), solvent: molecular biology grade DMSO solvent. Initially, 100 mL of phosphate buffer solution (PBS) has been prepared using pre-adjusted buffer tablet dissolved using distilled water. The enzyme concentrations (0.8 to 0.0125 U/mL) were prepared in PBS, alongside 4-nitrophenyl-D-glucopyranoside (pNPG) prepared in PBS (0.8 to 0.0125 mM), in addition test compounds and the standard were also prepared 100  $\mu$ M concentration in DMSO. A calibration graph constructed ( $r \geq 0.999$ ) plotted for the reaction mixture concentrations enzyme (0.1 U/mL) against substrate (0.8 to 0.0125 mM) at UV 405 nm. The screening was performed by measuring the absorbances of liberated *p*-nitrophenol (yellow) in sample/blank reaction mixtures at 405 nm. The total microplate well volume of 130  $\mu$ L that includes control (enzyme-120  $\mu$ L, phosphate buffer-5  $\mu$ L, phosphate buffer + substrate-5  $\mu$ L), reaction control blank (enzyme-120  $\mu$ L, phosphate buffer-10  $\mu$ L), reaction test (enzyme-120  $\mu$ L,

DMSO + test compound-5  $\mu\text{L}$ , phosphate buffer + substrate-5  $\mu\text{L}$ , reaction solvent blank (enzyme: 120  $\mu\text{L}$ , DMSO: 5  $\mu\text{L}$ , phosphate buffer + substrate-5  $\mu\text{L}$ ), reaction standard (enzyme-120  $\mu\text{L}$ , phosphate buffer + substrate-5  $\mu\text{L}$ , DMSO + voglibose-5  $\mu\text{L}$  (100  $\mu\text{M}$  to 0.5  $\mu\text{M}$ ). All the solutions were subjected to enzyme kinetics for 20 min to measure the absorbance. The percentage (%) enzyme inhibition calculated using the formula:  $(1 - \text{Absorbance of test compound} - \text{Absorbance of solvent blank} / \text{Absorbance of control} - \text{Absorbance of control blank}) \times 100$ . The statistical analysis was carried out using Microsoft Excel.

## RESULTS AND DISCUSSION

The chemical synthesis of rhodanine analogues was performed based on the Knoevenagel reaction conditions by treating the key intermediate [58,59], which is an addition product formed due to the reaction between 3-aminorhodanine and tosylisocyanate, as the first step. In second step, intermediate compound reacted with various substituted aldehydes to afford 5-benzylidene derivatives of rhodanine-sulfonylurea hybrid. The molecular structures of compounds **C-C13** were estimated initially based on the theoretical knowledge of the reaction products established. However, to confirm the molecular structure of the compounds, we used a set of spectroscopic methods and determined their structure. The combined spectroscopic data analysis from IR, NMR and mass revealed the molecular structures of compounds **C-C13**.

The high-resolution mass spectrometry (HRMS) in electrospray ionization technique was used to analyze the exact mass of compounds **C-C13** determined by negative ion mode using LC MS-grade methanol as a solvent. The HRMS mass spectra of compounds **C-C13** exposed the pseudo-molecular ion of their exact mass as M-H signal in negative mode. The M-H ion signals were revealed as base peaks, which are in good agreement with their relative molecular masses of the synthesized compounds **C-C13**.

Further, The FT-IR absorption spectra of compounds **C-C13** displayed a characteristic vibrational band at various frequencies associated with different types of functional groups present in the compound's basic nucleus. A sharp 'V'-shaped N-H stretching frequency was observed in all the compounds in the wavenumber ranging from 3030.17 to 3393.00  $\text{cm}^{-1}$ . A strong C=O stretching vibrational band was observed in all compounds within the range of 1680.00 to 1726.29  $\text{cm}^{-1}$ . In addition, a C=C stretching vibrational band was also observed in close proximity to the C=O as a coupling interaction within the range of 1517.98 to 1697.36  $\text{cm}^{-1}$ . The bending vibration of NH was also one of the important vibrational frequency bands observed in all compounds, in the range of 1527.62-1672.28  $\text{cm}^{-1}$ . The sulfonyl group displayed the symmetrical vibrational stretching bands ranging from 1309.67 to 1377.17  $\text{cm}^{-1}$ , while asymmetrical vibrations were observed within the range of 1112.93 to 1170.79  $\text{cm}^{-1}$ .

The  $^1\text{H}$  NMR spectra of compounds **C-C13** showed the presence of common types of protons such as aromatic methyl (Ar-CH<sub>3</sub>) of tosylurea, the three equivalent protons (Ar-CH<sub>3</sub>) resonated on the up-field as a singlet in the range of chemical shifts 2.48 to 2.49  $\delta$  ppm scale, consistently observed across

all compounds. The aromatic protons (Ar-H) of tosylurea and benzylidene moieties, the resonating frequencies ranging from 6.68 to 8.22  $\delta$  ppm scale, consistently observed across all the compounds. The amino protons of sulfonamido and carbox-amido groups which are part of sulfonylurea moiety resonated at significantly varied frequencies ranging from 5.91 to 5.93  $\delta$  ppm scale, not consistently observed across all compounds due to deuterium water exchange of amino protons. In compounds **C1-C13**, the characteristic benzylidene proton resonated as a singlet integrated for 1 proton, consistently among all derivatives at ranging from 7.71 to 7.96  $\delta$  ppm scale, which confirms that the phenyl ring substituent conjugated at position 5 of the rhodanine ring. In case of compound **C**, the ring characteristic reactive methylene group CH<sub>2</sub> protons of position 5 resonated at 4.20  $\delta$  ppm as a singlet peak integrated for two equivalent protons.

**In vitro bioassay:** The percentage inhibition values of the compounds indicate the measure of the effectiveness of each compound in targeting the  $\alpha$ -glucosidase enzyme. The  $\alpha$ -glucosidase inhibitory activity screening results are shown in Table-1, among the compounds screened, some of the compounds, **C** (64.86%), **C12** (58.32%), **C5** (57.74%), **C11** (51.38%), **C8** (48.56%), **C9** (46.43%), **C7** (45.75%), **C4** (44.73%) and **C6** (36.83%) showed relatively better potency than standard voglibose (37.75%); on the other hand, compound **C1** (37.62%) showed an almost similar range of potency. Subsequently, **C10** (33.45%), **C2** (23.66%), **C3** (13.25%) and **C13** (11.02%) were found to demonstrate moderate to poor levels of activity. The order of potency in descending order follows from compound **C** (64.86%) (hybrid), **C12** (58.32%) (3-bromo), **C5** (57.74%) (2-chloro), **C11** (51.38%) (2-bromo), **C8** (48.56%) (2-fluoro), **C9** (46.43%) (3-fluoro), **C7** (45.75%) (4-chloro), **C4** (44.73%) (4-dimethylamino), **C6** (36.83%) (3-chloro), voglibose (37.75%), **C1** (37.62%) (unsubstituted), **C10** (33.45%) (4-fluoro), **C2** (23.66%) (3-methoxyl), **C3** (13.25%) (2,4-dimethoxyl), **C13** (11.02%) (4-bromo), respectively.

The structure activity relationships (SARs) include compounds **C1-C13** with functional group substitution at different positions on the phenyl ring conjugated to position 5 of the rhodanine ring, which showed the variable levels of percentage inhibition of  $\alpha$ -glucosidase enzyme activity. The type of substituent on the phenyl ring influences the activity. The substituents, either electron-donating groups (EDG) or electron-withdrawing groups (EWG), on the phenyl ring conjugated to position 5 of rhodanine exhibit different inhibitory effects on the enzyme. Compounds with EDGs on phenyl ring showed relatively higher inhibition percentages compared to those with EWGs. The presence of specific functional groups substituent on phenyl ring, such as bromo, chloro, fluoro, methoxyl and dimethylamino, affected the inhibitory activity of the compounds. The compounds consisting of other groups such as 2-/3-/4-bromo, 2-/3-/4-chloro, 2-/3-/4-fluoro, 4-dimethylamino, 3-methoxyl and 2,4-dimethoxyl exhibit a good level of inhibition on enzyme activity. The positive control voglibose shows a moderate level of inhibition on the  $\alpha$ -glucosidase enzyme activity. The basic structural features of the compounds screened in the present study, consists of the rhodanine ring and also tosylurea linked

TABLE-1  
DATA OF PERCENTAGE INHIBITION OF THE  $\alpha$ -GLUCOSIDASE ENZYME ACTIVITY OF COMPOUNDS C-C13

Compound	% Inhibition of the $\alpha$ -glucosidase enzyme activity (100 $\mu$ M)	Structural features			
		Ring scaffold	Substituent on the 5-benzylidene-rhodanine	Type of substituent	N-substituent at the position 3 of rhodanine
C	64.86%	Rhodanine	–	–	Tosylurea
C1	37.62%	Rhodanine	–	–	Tosylurea
C2	23.66%	Rhodanine	3-Methoxyl	EDG	Tosylurea
C3	13.25%	Rhodanine	2,4-di-methoxyl	EDG	Tosylurea
C4	44.73%	Rhodanine	4-di-methyl-amino	EDG	Tosylurea
C5	57.74%	Rhodanine	2-chloro	EWG	Tosylurea
C6	36.83%	Rhodanine	3-chloro	EDG	Tosylurea
C7	45.75%	Rhodanine	4-chloro	EWG	Tosylurea
C8	48.56%	Rhodanine	2-fluoro	EDG	Tosylurea
C9	46.43%	Rhodanine	3-fluoro	EDG	Tosylurea
C10	33.45%	Rhodanine	4-fluoro	EDG	Tosylurea
C11	51.38%	Rhodanine	2-bromo	EDG	Tosylurea
C12	58.32%	Rhodanine	3-bromo	EDG	Tosylurea
C13	11.02%	Rhodanine	4-bromo	EDG	Tosylurea
Voglibose	37.75%				

EWG = Electron withdrawing group, EDG = Electron donating group.

to the nitrogen at position-3 of rhodanine ring, could be responsible for their inhibitory effects on the enzyme. The data provides insights into the SARs of compounds targeting the  $\alpha$ -glucosidase enzyme, highlighting the importance of specific substituents for modulating enzyme inhibition. The presence of rhodanine and a tosylurea group in all compounds suggested that these are common pharmacophores essential for compounds to inhibit enzyme activity. The results displayed that the position and nature of substituents on the rhodanine ring can significantly impact the inhibitory potency of the compounds. Compounds with similar structural features but different functional group substituents at various positions on the phenyl ring created a spectrum of bioactivity, highlighting the importance of structural modifications for specific enzyme inhibition. The above mentioned SAR helps in designing new compounds with prospective  $\alpha$ -glucosidase inhibitors. Further studies are needed to explore other substituent functional groups' role in enzyme inhibition. This discussion further provides valuable insights to design analogues of rhodanine-sulfonylurea hybrid derivatives as  $\alpha$ -glucosidase inhibitors and creates a direction for future research.

## Conclusion

In summary, this study provides an insight into the structure activity relationship (SAR) of 5-benzylidene analogues of rhodanine-sulfonylurea hybrid as a novel class of  $\alpha$ -glucosidase inhibitors. The inhibitory potencies exhibited by the compounds are primarily influenced by the nature of functional group substituent on the phenyl ring substituted at position 5 of the rhodanine ring. Compounds with electron-withdrawing groups typically exhibit greater potency; however, this observation has a limitation since there is another substituent group which was not studied, *i.e.* iodine. The findings of this study revealed a valuable insight for designing new hybrids as  $\alpha$ -glucosidase inhibitors consisting of rhodanine-sulfonylurea moiety since the bioassay results of compound C (4-methyl-N-((4-oxo-2-thioxothiazolidin-3-yl)carbamoyl)benzene-

sulfonamide) that has been further derived. Further research on derivatizing the hybrids with a more functional groups demonstrated a detailed SAR that contributes to the discovery of novel  $\alpha$ -glucosidase inhibitors.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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